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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,417	03/31/2004	Dale S. Dhanoa	24591-510 (PRE-10)	7662

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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/815,417	DHANOA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-22* is/are allowed.

6)☒ Claim(s) *23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 3/31/04. There are thirty-two claims pending and thirty-two under consideration. Claims 1-22 are compound claims. Claims 23-25 are composition claims. Claims 26-32 are method of using claims. This is the first action on the merits. The application concerns some thieno[2,3-d]pyrimidine compounds, compositions, and uses thereof.

Abstract

2. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable any physician skilled in the art of medicine to make claims 26-32 or use claims 23-25 of the invention. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The five main issues are the lack of any correlation between clinical efficacy for any disease treatment and Applicants' *in vitro* assay, the lack of guidance in the specification as to how the assays were performed, the state of the prior art, the unpredictability of the action of 5-HT_{2B} antagonists, and the breadth of the claims.

There is an *in vitro* assay, drawn to binding to the 5-HT_{2B} receptor, described tersely in lines 3-11 of page 93. The following Table has binding

data on 26 compounds. Exactly how this binding assay was performed in unclear. There are also entries in the Table for some functional data and some *in vivo* data on a few of the compounds but how this data was obtained is completely mysterious. There is no description of any assay used to obtain this *in vivo* data. Applicants do not state and it is not recognized in the CNS therapeutic arts this binding assay is correlated to clinical efficacy for the treatment of any human diseases.

The state of the clinical arts in 5-HT_{2B} receptor related diseases is provided by Poissonnett (Mini Rev. Med. Chem.), who states in their abstract that the precise role of the 5-HT_{2B} receptor has only recently emerged.

Doggrell (Expert Opin. Investig. Drugs) states on page 805 in the abstrcat that "antagonists at the 5-HT_{2B} receptor may reduce blood pressure". Applicants describe their compounds in lines 14-15, page 4 as antagonists at this receptor. However "may" is not the standard for enablement and Applicants have no data in their specification in any model of hypertension. Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 220 USPQ 924 concerning

the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry. Doggrell (Expert Opin. Investig. Drugs), in Figure 1, page 807 describes three known 5-HT_{2B} antagonists, SB224289, RS-127445, and LY-272015. No clinical uses of these three compounds are currently known. In section 4.7 on page 813 Doggrell (Expert Opin. Investig. Drugs) describes the effect of RS-127445 in a hypoxia mouse model of systolic blood pressure. This hypoxia mouse model is not a standard assay, predictive of human efficacy, but in any case, Applicants have no data from this hypoxia model.

Roth (Expert Opin. Ther.) in Table 2, page 686, lists diseases for which 5-HT subtype selective drugs have utility. Amitryptiline is the only antagonist at the the 5-HT_{2B} receptor listed. It has activity against pain. However, it is also listed as an antagonist at the 5-HT_{2A} receptor as well and Applicants have no data concerning the activity of their compounds at the 5-HT_{2A} receptor. In the passage in section 3, spanning pages 687-691, the author describes therapeutic uses of 5-HT_{2B}-selective drugs. However, a close reading of the passage reveals while both 5-HT_{2A} and 5-HT_{2C} seletive compounds have therapeutic utility, there is no mention of any 5-HT_{2B}-

selective compound. The unavoidable conclusion is that as of 2001, no such use was known.

Evidence of the unpredictability of the physiological activity of 5-HT_{2B} receptors is provided by Bonhous (British J. Pharmac.). In the first paragraph, second column, page 1075, their function in contacting smooth muscle in the intestine but relaxing the vascular tissue is noted. The authors concluding, "[5-HT_{2B} receptors] role in vascular tissue may be more complex". In the paragraph spanning pages 1079 to 1080, the effect of RS-127445, discussed above, in an organ bath experiment with rat juglar vein tissue is described. Alone the compound had no effect on this veinous tissue but, as an antagonist should, blocked the effect of an agonist. However, RS-127445 did reduce the maximal effect caused by the agonist, a-methyl-5-HT. Why this occurred in unexplained. A Google search failed to reveal any updated clincial results for RS-127445.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the hundred of diseases embraced by the term "CNS disorder". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught

one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Double Patenting

4. Claims 1-9, 11, and 22-32 of this application conflict with claims 1-29, 31, 34, 35, 36, 38-40, and 43 of Application No. 10/947,995. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822. The compound named in the present claim 11 is also named in claim 11 of Application No. 10/947,995. It is the sixth from the bottom of the list. Applicants have slightly altered the name of the compound but both names refer to the same chemical.

5. Claims 1, 4-9, 22, and 26-32 of this application conflict with claims 1, 2, 4, 6-8, and 11 of Application No. 11/075,565. 37 CFR 1.78(b) provides

that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822. The formula (II) of Application No. 11/075,565 is a simplified version of the present formula (I). However, working examples such as the present compounds 14 and 22 provide the guidance to arrive at this simper formula from the present formula (I)

Allowable Subject Matter

6. Claims 1-22 are allowed.

Conclusion

7. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center

(EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

8. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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TCMcK/me